REMARKS/ARGUMENTS

With entry of this amendment, claims 1-28 and 48-50 are currently pending in the above-identified application. Claim 49 is amended and new claim 50 is added as set forth in detail herein. No new matter is added. In view of the amendments and remarks set forth herein, reconsideration of all pending claims is respectfully requested.

Objections to the Specification

The Examiner objects to the specification as allegedly not including a reference to prior related applications as the first sentence of the specification. Applicants note that the specification was indeed previously amended to include the priority claim information. Specifically, Applicants refer the Examiner to the transmittal for the present application, as filed with Office on December 8, 2000, and which includes the following statement:

> Please amend this application by adding the following before the first sentence: "This application is a ... continuation of and claims the benefit of U.S. Application No. 08/462,749, filed on June 5, 1995, which is a continuation of U.S. Application No. 08/140,696, filed on October 21, 1993, which is a continuation of U.S. Application No. 07/532,429 filed on June 4, 1990, which is a continuation-in-part of U.S. Application No. 07/360,513, filed on June 2, 1989, the disclosure of which is incorporated herein by reference.
>
> [Application Transmittal as filed December 8, 2000.]

In view of the originally presented amendment to include the priority claim as quoted above, Applicants believe the present application fully complies with the requirements set forth in 37 C.F.R. § 1.78(a). In any event, by this Amendment, Applicants have re-presented the above-quoted amendment to the specification, updated to include the status of each priority application. In light the above, withdrawal of the objection is respectfully requested.

The Examiner has also noted the use of the trademarks Tween 20® and Sephadex® in the specification. The specification has been amended as requested to capitalize these terms and to include the generic terminology.

Rejections under 35 U.S.C. § 112, first paragraph

Claim 49 stands rejected under 35 U.S.C. §112, first paragraph, as allegedly not complying with the written description requirement. According to the Examiner, the specification does not support the limitation specifying a "latex bead entrapped on a microporous membrance" as being the solid phase onto which the peptide is immobilized. The Examiner further states that adequate written description exists for "a latex bead, and microporous membrane containing latex beads with a peptide immobilized onto the beads, wherein the peptide immobilized latex beads are entrapped in a microporous membrane," and invites Applicants to amend the claim accordingly. (Office Action dated 5/31/2006 at p. 4, ll.1-4.)

While Applicants do not agree with the rejection, but in order to further expedite prosecution of the instant application, claim 49 has been amended and new claim 50 has been added to essentially adopt the Examiner's suggestion. Claim 49 now recites "a latex bead" and new claim 50, which depends from claim 49, specifies that "wherein the latex bead, said bead having the immobilized peptide, is entrapped on a microporous membrane ...." In view of these amendments, withdrawal of the present rejection is respectfully requested.

Rejections under 35 U.S.C. § 103

Cosand '783 in view of Rosen and Storey

Claims 1-3, 7-9, and 48-49 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Cosand *et al.* (U.S. 4,629,783; "Cosand '783") in view of Rosen *et al.* (WO 87/06005; "Rosen") and Storey *et al.* (*J. Am. Chem. Soc.* 94:6170-6178, 1972; "Storey"). The Examiner states that the difference between the presently claimed invention and Cosand is that the thiol group of Cosand's peptide "is not reversibly protected from oxidation by a chemically reversible means, including ethylcarbamoyl, that is resistant to the highly acidic condition used during cleavage of the peptide from its synthesis solid support." (Office Action dated 5/31/2006 at p. 6, 2nd full para.) The Examiner further cites to Rosen as teaching "that peptides that

possess more than two cysteine residues may form cyclic monomers, linear to cyclic dimers, and linear polymers ... due to the reduction of the thiol group present on cysteine residues," and that the "cyclic monomer of the peptides is believed to be less efficient in binding the microtiter wells, and is less suited as a solid phase [ELISA] component." The Examiner then cites to Storey as teaching the use of ethylcarbamoyl to protect cysteine from highly acid cleavage conditions following synthesis. On this basis, the Examiner contends that one of skill in the art would have been motivated to use ethylcarbamoyl to reversibly protect the cysteine of Cosand's peptide from oxidation.

Applicants traverse the instant rejection. For the reasons set forth herein, a case of obviousness over Cosand, Rosen, and Storey has not been established with respect to the present claims. To support non-obviousness of the present claims, Applicants submit herewith the Declaration of Patrick Coleman under 37 C.F.R. § 1.132 (hereinafter the "Coleman Declaration"), together with supporting Exhibit 1. The Coleman Declaration addresses the Examiner's remarks in the Office Action and shows that the cited references would not lead one of ordinary skill in the art to the present invention. In particular, as shown by the Coleman Declaration and as further discussed herein, the cited references do not provide a sufficient motivation to the skilled artisan to achieve the claimed invention. In addition, non-obviousness is further shown by the commercial success of peptides according to the present invention.

A prima facie *case of obviousness over Cosand, Rosen, and Storey has not been established*

A *prima facie* case under 35 U.S.C. § 103 requires a clear and particular showing, in the prior art, of a motivation sufficient to impel one to do specifically what applicant has done. The Examiner must show, *inter alia*, some suggestion or motivation, either in the cited references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify a reference or combine reference teachings so as to achieve the specific combination as claimed by the applicant. *See* MPEP at §§ 2142 and 2143.01; *In re Fine*, 5 USPQ2d 1596, 1598, 1599 (Fed. Cir. 1988); *In re Dance*, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998). The suggestion or motivation to make the claimed combination must be found in the prior art and

cannot be based on applicant's disclosure. MPEP § 2142; *In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). The prior art reference(s) must be considered in their entirety, including portions that would teach away from the claimed invention. MPEP § 2141.03 (VI). Moreover, the proposed motivation must have sufficient "force" to "impel persons skilled in the art to do what applicant has done." *Ex parte Levengood*, 28 USPQ2d 1300, 1302 (Bd. Pat. App. Inter. 1993). The motivation must also be both objective and specific, *i.e.*, the Examiner's showing must be clear and particular. *See In re Dembiczak*, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999). It is this requirement for evidence of particularized motivation that provides a safeguard against the "tempting but forbidden zone of hindsight." *Id.* at 1616.

In the present case, the Examiner contends that a skilled artisan would have been motivated to modify Cosand as proposed so as to "control the oxidative form of peptides comprising more than one cysteine residue, and to provide a suitable solid phase component of the Enzyme-Linked Immunosorbent Assay (ELISA)." (Office Action dated 5/31/2006 at p. 7, 1st full para.) Contrary to the Examiner's assertion, for reasons further set forth herein, Cosand '783, Rosen, and Storey would not have led a skilled artisan to the peptide as presently recited in the claims. (*See* Coleman Declaration at ¶ 13 (emphasis provided).) None of these references, whether alone or in combination, teach or suggest the present invention's solution to a technical problem in the immunoassay art, nor otherwise teach or suggest a cysteine-containing, immobilized peptide as presently claimed in the application. (*Id.*)

First, Applicants note that the peptide composition as recited in independent claim 1 solves a technical problem in the area of immunoassay design. (Coleman Declaration at ¶ 14.) In particular, the oxidative form of a cysteine-containing peptide can influence antigenicity of the peptide when used in solid-phase immunoassays. The presently claimed invention allows for control over the oxidative form of a cysteine-containing peptide immobilized on a solid phase after cleavage and purification. (*Id.*) The present application states, *inter alia*, as follows regarding the technical problem addressed by the present invention:

> The presence of cysteine residues in a peptide allows for the formation of inter- and intra-molecular disulfide bonds during purification, immobilization, and upon long term

> storage of a deprotected peptide. Therefore, such peptide compositions are usually immobilized on a solid phase as a mixture of a variety of oxidative forms, including monomer, dimer and polymers of various sizes. Precautions are generally not taken to control the oxidative form of peptides immobilized on a solid phase.... The variety of oxidative forms of the peptides may be a source of variability in sensitive immunoassay and this may also influence the results based on those assays.
>
> [Application at p. 3, ll. 19-28, and p. 4, ll. 1-4.]

With particular regard to immunoreactivity, the formation of intramolecular (rather than intermolecular) disulfide bonds can contribute to the conformation of the peptide capable of binding antibodies engendered by the native protein. (Coleman Declaration at ¶ 15, citing application at p. 8, ll. 27-31.) Because an unprotected, cysteine-containing peptide will also form dimeric and polymeric oxidative forms, however, the proportion of the monomeric, intramolecularly disulfide-bonded ("cyclic") forms in a peptide mixture will be substantially lower than can be achieved with immobilized, reversibly protected peptides, which can be subjected to specific oxidation conditions in a more controlled manner. (*Id.* at ¶ 16.) Thus, as taught by the present application, hindering development of oxidative forms during synthesis of the peptide can allow for improved peptide immunological reactivity. (*Id.* at ¶ 17, citing application at p. 8, ll. 18-23.)

None of the cited references, however, address the problem discussed above, nor do these references otherwise provide a clear and particular motivation that would lead one of skill in the art to the invention as presently claimed. In particular, Cosand '783 does not teach or suggest, nor is Cosand '783 otherwise concerned with, controlling the oxidative form of a cysteine-containing peptide. (Colemen Declaration at ¶ 18.) Cosand discloses new (gag and env) peptide compositions, including, *e.g.*, cysteine containing peptide 39 (peptide V). Cosand '783, however, does not discuss the various oxidative forms of the disclosed peptides and the influence of such oxidative forms in immunological assays. (*Id.*) Indeed, in regard to the use of the disclosed peptides in HIV immunoassays, Cosand '783 shows peptide V, when immobilized, to be very reactive with LAV antibodies. (*Id.* at ¶ 19, citing Cosand '783 at Tables I and III.)

Cosand '783 does not discuss any deficiencies of peptide V, or any other cysteine-containing peptide, that would specifically suggest to the skilled artisan to reversibly protect the cysteines during the peptide's cleavage, purification, and immobilization on a solid phase for use in immunoassays. Thus, the skilled artisan reading Cosand '783 would understand the immunoassay methods as disclosed therein to be specific and self-sufficient. (Coleman Declaration at ¶ 19.) For these reasons, Cosand does not provide any clear and particular motivation to modify the peptides disclosed therein in a manner that would lead to the presently claimed invention. (*Id.* at ¶ 20.)

In the case of Rosen, although this reference briefly discusses the presence of various oxidative forms in immobilized, cysteine-containing peptides, Rosen does not provide a solution. (Coleman Declaration at ¶ 21.) In fact, Rosen actually teaches away from the present invention by teaching that polymeric oxidative forms are advantageous over the cyclic, monomeric forms. In this respect, Rosen states as follows:

> The cyclic monomer form, while retaining a portion of the antigenicity of the polymer form, is believed to be less efficient in binding to the microtiter wells and is less suited as the solid phase component of the ELISA.
>
> [Rosen at p. 22, ll. 27-31.]

In view of this disclosure, Rosen does not provide any clear and particular motivation to the skilled artisan to modify Cosand '783, in the manner proposed by the Examiner, so as to achieve the claimed invention. (Coleman Declaration at ¶ 22.) To the contrary, Rosen would instead suggest to the skilled artisan that the proportion of the polymeric oxidative form should be increased, which could not be achieved by reversibly protecting a cysteine-containing peptide. (*Id.*) The skilled artisan reading Rosen would thus be led to maintain the peptide in a deprotected state to facilitate formation of the polymeric oxidative form prior to immobilization, and further to control the proportion of the polymeric form by adjusting the oxidative conditions with respect to temperature, pH, peptide concentration, and the like, as explicitly suggested by Rosen. (*Id.*, citing Rosen at p. 22, l. 35, to p. 23, l. 4.)

Storey does not remedy the deficiencies of Cosand and Rosen as discussed above. (Coleman Declaration at ¶ 23.) Storey is an academic, organic-chemistry-oriented article concerned with finding new ways of synthesizing polypeptides, particularly polypeptides derived from a ribonuclease of about 80 amino acids in length, the polypeptides being constructed from separately synthesized, protected peptides. (*Id.*, citing Storey at, *e.g.*, Abstract.) Storey does not discuss, however, the influence of reversibly protecting cysteine thiol groups on antigenicity, nor does Storey discuss the diagnostic importance of controlling disulfide bond formation when preparing peptide reagents for immunoassay. (Coleman Declaration at ¶ 23.) Storey does not discuss or otherwise suggest that using the S-ethylcarbamoyl group would be useful or advantageous in the synthesis of a peptide for use as an antigen. (*Id.*) For these reasons, Storey also fails to provide any clear and particular motivation to the skilled artisan to modify the peptide of Cosand '783 in the manner proposed by the Examiner, so as to achieve the presently claimed invention. (*Id.* at ¶ 24.)

For at least the reasons set forth above, a *prima facie* case of obviousness has not been established with respect to the claims 1-3, 7-9, and 48-49 over Cosand '783, Rosen, and Storey. As previously noted, a *prima facie* case of obviousness requires a showing of a clear and particular motivation, in the cited art itself, sufficient to lead the skilled artisan to do what Applicants have done. Here, as set forth above, none of the cited references provide such a specific motivation. To the contrary, when the references are considered in their entirety, as required by the MPEP and current case law, then the references actually teach away from the claimed invention, as discussed above with respect to Rosen. Therefore, because a *prima facie* case of obviousness has not been established, withdrawal of the present rejection is respectfully requested.

Non-obviousness is further shown by the commercial success of immunoassays employing peptide compositions according to the present invention

In addition to the lack of any teaching or suggestion of the presently claimed invention in the references cited in the Office Action, the presently claimed invention has led to

the commercial success of immunoassay products manufactured and distributed by Bio-Rad Laboratories ("Bio-Rad"), the assignee of the present application. (Colement Declaration at ¶ 26.) Bio-Rad's immunoassay products include two licensed blood screening products, licensed by the United States Food and Drug Administration ("FDA"), for detection of HIV that employ peptides as presently claimed in the present application. (Coleman Declaration at ¶ 29.) These products are the HIV-1/HIV-2 Synthetic Peptide EIA ("Peptide EIA") and the Multispot HIV-1/HIV2 Rapid Test ("Rapid Test"). (*Id.*) The success of these products on marketplace can be substantially attributed to the peptide technology as defined in the present claims. (*See* Coleman Declaration, ¶¶ 30-38.) Accordingly, because commercial success is further, objective indicia of non-obviousness (*see, e.g.*, MPEP § 2144.08(II)(B) (citing cases)), the presently claimed invention is patentable over the Cosand, Rosen, and Storey in addition to the reasons set forth above.

The Peptide EIA was licensed by the FDA in August, 1997, and still remains on the market today. (Coleman Declaration at ¶ 30.) This product has been used to screen blood and plasma for the presence of HIV antibodies since its approval. It has been one of two FDA-licensed assays used to safeguard the U.S. blood/plasma supply over the last nine years. Over this period, nearly 100 million tests have been sold, with a total sales revenue of over $100 million. By any standard in the industry, the Peptide EIA has been commercially successful, and an important product in the U.S. marketplace. (*Id.*)

The Rapid Test is designed to diagnose HIV infection and, in particular, to differentiate between an HIV-1 infection and an HIV-2 infection. (Coleman Declaration at ¶ 31.) It is run in a totally manual mode and is not intended for any high volume blood screening application. It can be run in a field hospital as well as in a standard laboratory. At the time the Rapid Test was first developed, because the FDA was not ready to approve any rapid HIV test, the Rapid Test was initially not approved by FDA for sale and use in the U.S. Instead, this technology was transferred to France, where it was manufactured, and the kits were sold in many countries, especially in African nations. After several years, the production of the Rapid Test kits was transferred back to the U.S. and it has been approved by the FDA for U.S. distribution.

To date, the Rapid Test is the only commercial product for the detection and differentiation of HIV-1 and HIV-2 infections. This product has had a great world-wide reputation, and it has been used and promoted by the Centers for Disease Control (CDC). The Rapid Test has been extremely useful in tracking the incidence of HIV-2 infections in the U.S. population. Although its usage volume is expectedly much lower and it is not intended for blood screening, total sales revenue in France is approximately $10 million, and, since its entry into the U.S. marketplace in 2005, total U.S. sales revenue is nearly $3 million. Thus, the Rapid Test has also been commercially successful and an important product in the marketplace. (*Id.*)

Both the Peptide EIA and the Rapid Test have high sensitivity and produce highly accurate results, which have contributed to their success in the HIV field. (Coleman Declaration at ¶ 32.) The high sensitivity and accuracy of the Peptide EIA and Rapid Test can be attributed, *inter alia*, to the technology as presently embodied in claim 1 of the present application. (*Id.* at ¶ 33.) In particular, each of the Peptide EIA and Rapid Test employ, *inter alia*, peptides having an amino acid sequence of six to 50 amino acids, the sequence comprising two cysteine residues which are separated from each other by at least two but fewer than twenty non-cysteine amino acid residues. (*Id.* at ¶ 34.) These peptides include peptides derived from the HIV transmembrane proteins HIV-1 gp41 and HIV-2 gp36. The peptides range in size from 17 amino acid residues to 35 amino acid residues and include native cysteines separated by 5 amino acid residues. (*Id.*) During synthesis of these peptides (*see* ¶ 34) on a synthesis solid support, as well as during subsequent cleavage, the native cysteines are reversibly protected from oxidation with an ethylcarbamoyl (EC) group, which is a chemically reversible protection means resistant to the highly acidic conditions used to cleave the peptides from the solid support. (*Id.* at ¶ 35.)

The use of the chemically reversible protection means in manufacturing the Peptide EIA and Rapid Test, as discussed above, allows the oxidative state of the peptide to be controlled during formation of the immunoassay solid phase. (Coleman Declaration at ¶ 36.) The cysteines are prevented from forming the cyclic, epitope structure, until after the peptides are immobilized on their respective solid phases. In particular, because the cysteine thiols have been protected during synthesis, cleavage, and purification, polymeric oxidative forms of the

peptides are substantially minimized. Once immobilized on the solid phase, deprotection of the peptide, together with the application of appropriate oxidation conditions, allows the peptide to be maintained in a purified, cyclic (intramolecularly disulfide-bonded) form. (*Id.*)

It is the purified, cyclic form of these peptides (employed in the Peptide EIA and Rapid Test) that has improved immunological reactivity over other oxidative forms. (Coleman Declaration at ¶ 37.) In particular, it is the purified, cyclic form of the peptides that confers much of the high specificity and sensitivity of the Peptide EIA and Rapid Test, as well as the accuracy of the results. Immune recognition of the immobilized peptides, by natural HIV antibodies, is poor or absent prior to the removal of the EC groups. After removal of the protecting groups, cyclization of the cysteine loops, and dimer formation, the specific immune recognition increases dramatically. This demonstration of the sensitivity to the detection of HIV antibodies was critical for achieving FDA approval and, as previously indicated above, the high sensitivity and accuracy of these immunoassays has contributed to their success in the HIV field. (*Id.*)

Furthermore, preventing the formation of disulfide bonds during cleavage from the synthesis solid phase, and subsequent handling of the peptides during kit manufacturing operations, was also critical for meeting necessary FDA license criteria for peptide characterization. (Coleman Declaration at ¶ 38.) To receive FDA approval for the HIV peptides used in the Peptide EIA and Rapid Test, it was necessary to demonstrate the consistency and purity of the peptides, including these properties *vis-à-vis* their oxidative state once immobilized on the solid phase. Such consistency and purity was achieved by preventing random, sulfhydryl redox chemistry during peptide cleavage and subsequent handling, as discussed above. To create a manufacturable solid phase, controlled deprotection of the reversible blocking groups was employed once the peptides were applied to the microplate or latex bead solid phases. Thus, peptide compositions as presently embodied in the '239 claims were important in leading to FDA approval of the Peptide EIA and Rapid Test immunoassays, and as well as their commercial success. (*Id.*)

Accordingly, for the reasons above, in addition to the reasons previously set forth, because the commercial success of certain FDA-licensed immunoassay products can be attributed to the presently claimed invention, claims 1-3, 7-9, and 48-49 are non-obvious over Cosand '783, Rosen, and Storey. Withdrawal of the present rejection is again respectfully requested.

Cosand '783 in view of Rosen, Storey, and Cosand '211

Claims 1, 4-6, 8-13 stand rejected under 35 U.S.C. §103 as allegedly unpatentable over Cosand '783 in view of Rosen and Storey, as applied to claims 1, 8, and 9, in further view of Cosand *et al.* (U.S. Patent No. 5,075,211; "Cosand '211").

Applicants traverse this rejection. Cosand '211 does not remedy the deficiencies of Cosand '783, Rosen, and Storey as previously discussed above. (Coleman Declaration at ¶25.) The Examiner cites to teaching, *inter alia*, the "use of cysteine in combination of other intervening amino acid spacers." (Office Action dated 5/31/2006 at p. 8, last para.) Cosand '211 does not discuss or otherwise suggest, however, the influence of reversibly protecting cysteine thiol groups on antigenicity, nor does Cosand '211 discuss the diagnostic importance of keeping cysteine thiol groups protected when preparing peptide reagents for immunoassay. (Coleman Declaration at ¶ 25.) Therefore, Cosand '211 does not provide any clear and particular motiviation to modify the peptide of Cosand '783 so as to achieve the presently claimed invention. (*Id.*)

For at least these reasons, because a *prima facie* case under 35 U.S.C. § 103 has not been establish with respect to Cosand '783, Rosen, and Storey, and because Cosand '211 does not address the previously discussed deficiencies of these other references, a *prima facie* case has not been established with respect to the combination of Cosand '783, Rosen, Storey, and Cosand '211. Applicants further note that, because the commercial success of certain FDA-licensed immunoassay products can be attributed at least partly to the technical features of independent claim 1, which is an objective inidicia of non-obviousness, claims 1, 8, and 9 are non-obvious

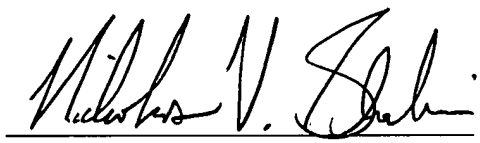
over the combination of these four references for at least this reason as well. Accordingly, withdrawal of the present rejection is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,

Date: November 28, 2006 By: 

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Attachments: Declaration of Patrick Coleman under 37 C.F.R. § 1.132 with supporting Exhibit 1

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